What’s up with IGRAs?

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Agenda

- High Level Comparison of IGRAs
- Clinical Study Review
- Pre-Analytical Differences
- Effect of Patient Specific Factors
- Leveraging Data
- Future of the T-SPOT.*TB* Test

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Comparison of Commercially Available IGRAs

Variables	QuantiFERON-TB Gold	QuantiFERON-TB Gold-Plus	T-SPOT.TB Test
Technology	ELISA	ELISA	ELISPOT
Test Substrate	Whole blood	Whole blood	Peripheral blood mononuclear cells
Sample Collection	3 specialized tubes	4 specialized tubes	1 standard tube
Adjusted Cell Count	No	No	Yes
Cell Wash	No	No	Yes
Cell Targets	CD4	CD4, CD8	CD4, CD8
Sample Stability	16 hours	12 hours (may be stored in 2–8 °C for 16 to 48 hours)	32 hours
Diagnostic Performance	Package Insert: sensitivity, 88.7%; specificity, 99.2%	Package Insert: Sensitivity in US 88.7%, 94.8% including Japan and Australia; specificity in US 98.1%, 97.3% including Japan and Australia	Package Insert: sensitivity, 95.6%; specificity, 97.1%
Readout	Interferon-gamma concentration (international units per mL)	Interferon-gamma concentration (international units per mL)	Individual spots representing captured interferon-gamma
Result Interpretation	Positive, Negative, Indeterminate	Positive, Negative, Indeterminate	Positive, Borderline, Negative, Invalid Includes FDA-approved borderline category

Reliable and Repeatable Results

The T-SPOT.*TB* Test Results	ODL National Average
Positive	4.2%
Negative	93.1%
Borderline	1.9%
Invalid	0.7%

Based on Oxford Diagnostic Laboratories prior 12 month data (March 2016 – February 2017.
Oxford Diagnostic Laboratories Data. Memphis, TN 2016-2017.

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QFT-GIT and T-SPOT.*TB* Test Sensitivity
Summary of Head-to-Head Studies in Confirmed TB

- Demonstrates T-SPOT.*TB* test is more sensitive than QFT-GIT
  - TB confirmed through direct detection of MTB via culture or PCR
  - Updated 08/03/2015
  - Analysis based on peer-reviewed articles published between 01/01/2007 and update date
  - Indeterminate [invalid] results excluded prior to sensitivity calculation, but not quantified within the article are listed as excluded
  - NR indicates indeterminate [invalid] results not reported within the article
  - Sensitivity for T-SPOT.*TB* higher in 9/14 publications (64.3%)

Publication	T-SPOT.*TB* Test		QFT-GIT	
	Sensitivity % (n/N)	Invalid [Indeterminate] % (n)	Sensitivity % (n/N)	Indeterminate % (n)
Detjen *Clin Infect Dis*, 2007.	92.9 (26/28)	0 (0)	92.9 (26/28)	0 (0)
Chee *J Clin Microbiol*, 2008.	92.7 (254/274)	1.5 (4)	81.8 (224/274)	10 (3.6)
Domínguez *Diagn Microbiol Infect Dis*, 2009.	84.2 (32/38)	5.3 (2)	71.1 (27/38)	2.6 (1)
Kampmann *Eur Respir J,* 2009.	58.3 (14/24)	0 (0)	80.0 (20/25)	8.0 (2)
Latorre. *Diagn Microbiol Infect Dis*, 2009.	94.9 (37/39)	NR	85.0 (34/40)	NR
Markova *Biotechnol. & Biotechnol. Eq*, 2009.	61.5 (8/13)	30.8 (4)	92.3 (12/13)	0 (0)
Lai *Eur J Clin Microbiol Infect Dis*, 2011.	87.8 (86/98)	0 (0)	65.3 (64/98)	6.1 (6)
Ling *Eur Respir J*, 2011.	84.1 (116/138)	0.7 (1)	76.1 (105/138)	11.6 (16)
Kobashi *Intern Med*, 2012.	95.5 (21/22)	0 (0)	86.4 (19/22)	4.5 (1)
Theron *Eur Respir J,* 2012.	85.0 (91/107)	excluded	84.9 (90/106)	excluded
Chiappini *Pediatr Infect Dis J,* 2014.	75.0 (21/28)	0 (0)	89.3 (25/28)	0 (0)
Kobashi *OJRD*, 2014.	91.7 (11/12)	0 (0.)	83.3 (10/12)	8.3 (1)
Young *Eur Respir J*, 2014.	61.9 (13/21)	28.6 (6)	61.9 (13/21)	33.3 (7)
Yu *Medicine,* 2015.	95.8 (46/48)	NR	70.8 (34/48)	NR
Total	**87.2% (776/890)**	**2.4% (17)**	**78.9% (703/891)**	**6.3% (44)**

Clinical Superiority of the T-SPOT.*TB* Test

Increased Sensitivity Cited in Guidelines

- US CDC/ATS/IDSA Guidelines

  "In individuals who are likely to be infected with *Mtb* but at low or intermediate risk of disease progression, **the sensitivity of IGRAs** in the detection of *Mtb* infection has been consistently reported at **either equal (QFT; 81%-86%) or superior (T-SPOT; 90-95%)** to the sensitivity of the TST (71%-82%) when either a final diagnosis of either microbiologically confirmed or clinical TB is used as the reference standard."

- USPSTF Guidelines

  USPSTF presented pooled sensitivity estimates of all four LTBI tests in its evidence report supporting the most recent TB screening and treatment recommendation

Test	# Studies	# Participants	Pooled Sensitivity Estimates (95% CI)
TST (10 mm threshold)	11	988	79% (71 – 87%)
The T-SPOT.TB test	16	984	90% (87 – 93%)
QuantiFERON TB Gold	17	1,073	77% (74 -- 81%)
QuantiFERON TB Gold In-Tube	24	2,321	80% (77 – 84%)

Sources:
https://www.cdc.gov/tb/publications/guidelines/pdf/cid_ciw694_full.pdf;
https://jamanetwork.com/journals/jama/fullarticle/2547762

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Comparison of the Sensitivity of T-SPOT.*TB* and QFT-GIT According to Patient Age

- Retrospective review of medical records of diagnosed TB patients
  - diagnosed with active pulmonary or extrapulmonary TB
  - in Seoul, Korea from February 2008 to December 2013
  - defined as active TB based on either a positive culture or a positive PCR

Test	Sensitivity of IGRAs across age group					Result of IGRA		
	≤29 years	30-49 years	50-69 years	≥70 years	Overall	Positive	Negative	Indeterminate
T-SPOT.*TB* (n = 212)	96.7%	94.7%	87.5%	85.7%	91.0%	193 (91.0)	15 (7.1)	4 (1.9)
QFT-GIT (n = 192)	93.3%	86.5%	76.8%	68.3%	80.2%	154 (80.2)	23 (12)	15 (7.8)

"QFT-GIT, but not T-SPOT.TB, was significantly affected by patient age"

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Bae W, Park KU, Song EY, et al. Comparison of the Sensitivity of QuantiFERON-TB Gold In-Tube and T-SPOT.TB According to Patient Age. Shams H, ed. *PLOS ONE*. 2016;11(6):e0156917.

Head-to-head studies between QuantiFERON®-TB Gold (QFT®) and QuantiFERON-TB Gold Plus (QFT-Plus)

Publication	Sensitivity % (n/N)		Comments
	QFT	QFT-Plus	
Yi. Sci Rep, 2016.	93.6 (147/157)	91.1 (143/157)	Active TB
Hoffmann. Clin Microbiol Infect, 2016.	89.5 (51/57)	89.5 (51/57)	Active TB
Petruccioli. Journal of Infection, 2016.	89 (24/27)	85 (23/27)	Active TB
Petruccioli. Tuberculosis, 2017.	88 (61/69) 100 (58/58) 73 (24/33)	90 (62/69) 98 (57/58) 82 (27/33)	Active TB LTBI Cured TB
Takasaki, Journal of Infection and Chemotherapy, 2018.	98 (97/99)	99 (98/99)	Active TB

Search dates: 2016-2018
Last update: July 2018

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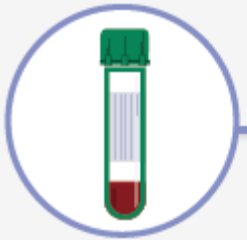
Pre-Analytical Steps

The T-SPOT.TB test



The T-SPOT.*TB* test solution:
By utilizing standard phlebotomy practices and ensuring that all up-front processing of the specimen after blood draw is done in a laboratory setting, controlled conditions are leveraged to mitigate impact of confounding variables associated with pre-analytical complexity.

QuantiFERON technology

Volume requirement

Since the QuantiFERON procedure does not standardize for cell count prior to antigen stimulation, volume can have direct impact on IFN-gamma release.[18,19] Studies conducted on the QFT-Gold format have shown that even within the validated .8 - 1.2 mL range, a patient's result can experience a 30% difference in the positivity rate depending on the blood volume collected.[20]

Table 1[16]

Blood volume (mL)	Positive Results from infected subjects (%) (n/N)
0.8	88.2 (15/17)
1.0	70.6 (12/17)
1.2	58.8 (10/17)

Effect of incubation delay

Though various workflows have been introduced with QFT-Plus, the lack of changes in test procedure leaves opportunity for QuantiFERON's pre-analytical steps to continue to impact results. In fact, a warning exists in the QFT-Plus package insert stating "delay in incubation may cause false negative or indeterminate results."[18] Similarly, studies conducted on the QFT-Gold format have shown that even within the recommended time frame for incubation, false-negative or indeterminate results increase with time.[20, 21, 22]

Table 2[21]

Incubation delay	Mean IFN-gamma produced n=126	Number of positive results
0 hours	0.77 IU/mL	26
6 hours	0.35 IU/mL	20
12 hours	0.19 IU/mL	17

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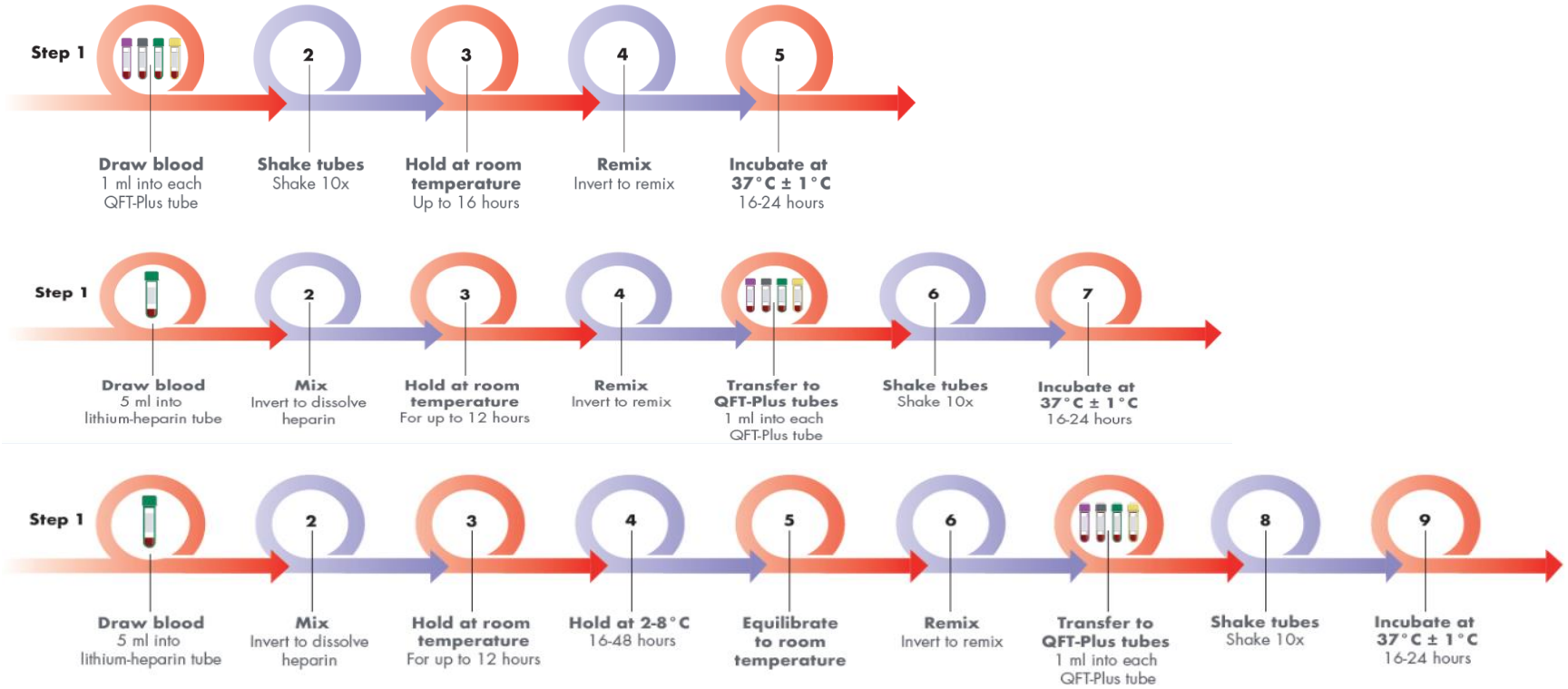
New Blood Draw Options for QFT- Plus



QuantiFERON®-TB Gold Plus (QFT®-Plus) Package Insert. 1095849 Rev. 02

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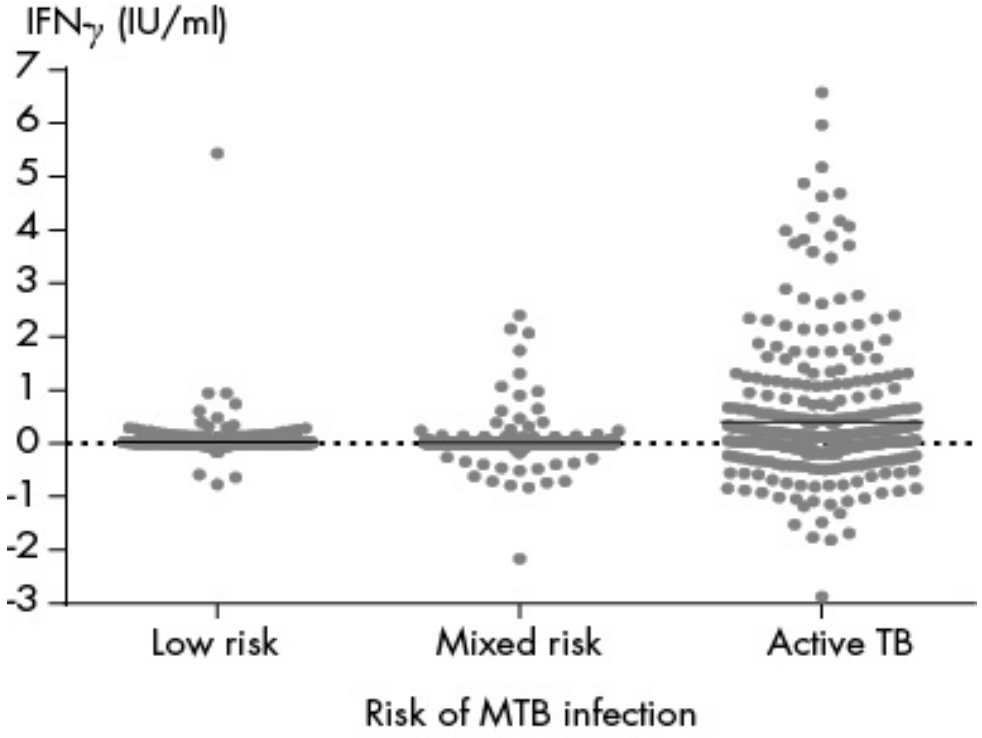
QFT-Plus sample variability



Proof Source:

- QFT-Plus package insert (pg. 53)

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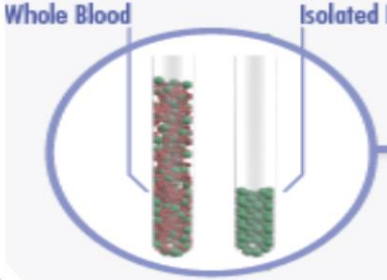
Effect of Patient Specific Factors

The T-SPOT.TB test



The T-SPOT.*TB* test solution:
The T-SPOT.*TB* test separates peripheral blood mononuclear cells (PBMCs) from whole blood and standardizes the number of these cells used in each patient test, reducing the risk of false-negative and invalid test results due to abnormal patient cell counts.[1] The test also includes multiple washing steps which enable the removal of potentially interfering substances that can affect test results, such as certain drugs and endogenous IFN-gamma.[1,23]

QuantiFERON technology

Immune system differences:
Patients have variations in their white blood cell counts, including T cell lymphocytes. Since QFT measures T cell response, but does not standardize the number of cells per test, the variations in cell count may influence results. The manufacturer states, "The effect of lymphocyte count on reliability of QFT results is unknown … The minimum number of lymphocytes required for a reliable test result has not been established and may also be variable."[18]

Patient's medications:
Since T cells are stimulated in whole blood, circulating immunosuppressive drugs have the ability to interfere with the test's results. Multiple studies have shown that the QuantiFERON technology may be affected in patients on steroid therapy.[24,25] For instance, steroid use has been associated with indeterminate test results and negatively associated with a positive QFT-Gold result.[25] QFT-Plus has not been extensively evaluated in this population, among others, so the impact on this format is still being explored.[18]

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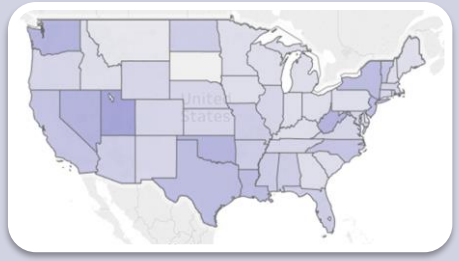
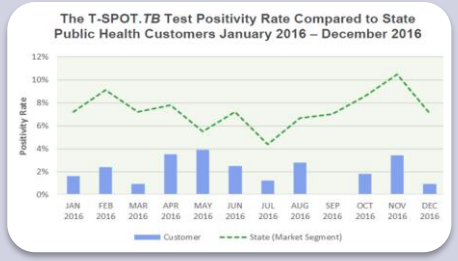
Applying Data to Reduce Active Cases





Find Latent TB

Track Screening Results

Treat Latent TB in Groups Likely to Progress

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Questions?

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